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Effects of Environmental Tobacco Smoke Exposure on Pulmonary Function and Respiratory Health in Adults: Update 1997

Key Words

Environmental tobacco smoke
Spousal/household smoking
Pulmonary function
Respiratory health

Abstract

Eighteen epidemiology studies have examined the relationship between chronic environmental tobacco smoke (ETS) exposure and pulmonary function. A statistically significant relationship between chronic ETS exposure and a specific spirometric endpoint was reported in 5 of 17 studies that measured forced expiratory volume in 1 s (FEV_1), 2 of 9 studies that measured forced vital capacity (FVC) and 3 of 5 studies that measured mean forced expiratory flow during the middle half of the FVC. Fourteen of 24 epidemiological studies report a statistically significant association between chronic ETS exposure and a clinical endpoint, although there is little consistency from one report to the next when a specific endpoint is considered. A statistically significant association was reported in 2 of 9 studies for cough, 3 of 9 studies for phlegm and expectoration, 6 of 10 studies for dyspnea and shortness of breath, 3 of 6 studies for bronchitis, and 8 of 18 studies dealing with asthma incidence, exacerbation, or symptoms. The inconsistency of association in the foregoing functional and clinical epidemiology studies could either reflect absence of such an association or methodology problems such as reliability of spirometric measurement, lack of verification of clinical endpoint, errors in classification of smoking and ETS exposure status and inappropriate control of confounding variables. The effects of acute ETS exposure (at levels equivalent to or exceeding real-life smoke-polluted environments) have been examined in experimental studies in which spirometric measures were obtained prior to, during, and after exposure of subjects to machine-generated tobacco smoke. Six of seven studies suggest that acute ETS exposure, while serving as an irritant to the upper respiratory tract, fails adversely to affect pulmonary function of normal adults. The effect of acute ETS exposure in asthmatic subjects has been examined in 15 studies. These studies suggest that acute exposure to ETS does not consistently evoke adverse pulmonary effects in most asthmatics. Several studies from a single research group suggest that a small sub-set of asthmatics may respond to acute ETS exposure with a $\geq 20\%$ decrement in FEV_1 as well as an increased responsiveness to bronchoconstrictors. The mechanism for this responsiveness does not appear to be allergic in nature and is subject to speculation.

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Introduction

A major area of interest concerning the health effects of environmental tobacco smoke (ETS) other than lung cancer is that relating to its non-cancerous effects on the respiratory system. A relatively large series of studies have attempted to relate ETS exposure in children and pulmonary function and respiratory symptoms and diseases. These have been previously reviewed by us [1–3].

Compared to studies in children, relatively few studies exist in the literature pertaining to the effects of ETS on the respiratory system of adults. The 1986 reports of United States Surgeon General [4] and the National Research Council of the National Academy of Sciences [5] on environmental tobacco smoke both concluded that there were insufficient data to determine whether ETS exposure adversely affected pulmonary function and respiratory health in adults. The issue of ETS and the respiratory system of adults was reviewed by us several years after the above-referenced 1986 consensus reports [6, 7]. As indicated in our reviews, several different approaches to the study of effects of ETS on the respiratory system of adult subjects have been employed: (1) epidemiology studies dealing with effects of chronic ETS exposure on pulmonary function; (2) epidemiology studies dealing with effects of chronic ETS exposure on respiratory symptoms (e.g., cough, phlegm, wheeze) and disease (chronic obstructive pulmonary disease), and (3) experimental studies of acute effects of ETS on pulmonary function in normal and asthmatic adults. Based upon the available studies at that time, we concluded that there were no consistent data supporting an association between chronic ETS exposure and impaired pulmonary function or increased incidence of respiratory symptoms and diseases in adults. We also concluded that there was little or no evidence that acute ETS exposure impairs pulmonary function in normal individuals. While there was no conclusive evidence that acute ETS exposure adversely affected most asthmatic adults, a subpopulation of asthmatics may exist which is susceptible to such exposures [6, 7].

Since our last reviews on the subject of ETS exposure and the respiratory system of adults, there has been a considerable increase in the number of reports that have addressed the issue. In view of the increased activity in this area, the purpose of the present review is to reexamine the issue of respiratory health effects of ETS in adults.

Epidemiology Studies of the Association between Chronic ETS Exposure and Non- Neoplastic Respiratory Effects in Adults

In general, these studies attempted to determine whether a statistically significant association existed between chronic ETS exposure of a non-smoking subject and an adverse effect on the respiratory system. Smoking status (e.g., smoker, ex-smoker, non-smoker, or never-smoker) and exposure status (e.g., ETS exposed vs. non-exposed) of the subject were usually determined by a questionnaire (either self-administered or interviewer-assisted). Among the criteria for classifying an individual as ETS exposed were the presence of a smoking spouse, other smokers in the household, and/or exposure to tobacco smoke at work. Such criteria varied from study to study. The questionnaire was also used to obtain information on the subjects' previous health history and other potential confounding variables.

When pulmonary function was the endpoint, the determinant of adverse effect was a statistically significant decrement in some spirometric parameter derived from the forced vital capacity (FVC) or the amount of air that can be expelled from the lungs by a maximum forced expiratory effort after a maximum forced inspiratory effort [7]. The most frequently used such parameter is FEV_1 (forced expiratory volume in 1 s) or the volume of air expelled during the first 1 s of the FVC manoeuvre. Another frequently used measure is FEF_{25-75} or the rate of the airflow during the mid-portion (between 25 and 75%) of the FVC. Other less frequently used parameters are also derived from or related to the FVC, such as PEFR (peak expiratory flow rate), or MEF (maximum expiratory flow) at some portion of the FVC (25, 50, 75%), or some other portion of the FEF (75–85%).

When clinical endpoints were of interest, these studies sought to determine whether a statistically significant association existed between chronic exposure to ETS and increased incidence of a respiratory symptom (such as cough, wheeze, phlegm) or a disease (such as bronchitis, chronic obstructive pulmonary disease, or asthma).

As noted below some of the studies examined both spirometric and clinical endpoints.

Pulmonary Function

Our initial reviews [6, 7] of the epidemiology literature relating ETS exposure to pulmonary function in adults involved the first 12 studies listed in table 1 [8–19]. Since that time an additional 6 studies have been published [20–25]. As shown in table 1, the most prominent param

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Table 1. Epidemiology studies of ETS exposure and pulmonary function in adults

Study [ref.]	FEV_1	FVC	FEF_{25-75}	Other observations and number of subjects
Schilling et al. 1977 [8]	NC (0 to −7%)[1,3]	NC	NR	NC PEF: n = 212 (74 ETS exposed) F and 178 (40 ETS exposed) M
White and Froeb 1977 [9]	NC (−5 to −6%)[5]	NC (−3 to −4%)	decr. (−13 to −15%)	decr. FEF_{75-85} (−20 to −25%), n = 400 (200 ETS exposed) F and 400 (200 ETS exposed) M
Comstock et al. 1981 [10]	NC	NC	NR	n = 49 (15 ETS exposed) F, 369 (78 ETS exposed) M
Kauffmann et al. 1983 [11]	NC (−1 to −2%)	NC (−1% to −3%)	NC (−1 to −4%)	F >40 y, decr. FEV_1 (−4%), FVC (−3%), FEF_{25-75} (−6%); M >40 y, not significant for FEV_1 (+7%), FVC (−4%) and decr. FEF_{25-75} (−16%); n = 2,084 (826 ETS exposed) F and 914 (65 ETS exposed) M
Salem et al. 1984 [12]	NC (−6%)	NR	NR	NC in PEF (−3%), $FEV_{1\%}$ (−2%); decr. air velocity index (−10%); incr. total expiratory time (31%); n = 349 (219 ETS exposed)
Lebowitz 1984 [13]	NR	NR	NR	NC PEF (n not reported)
Kentner et al. 1984; Kentner and Weltle 1988 [14]	NC	NC (0 to −2%)[2]	NC (+1 to −5%)[2]	NC for PEF, MEF_{25-75}, $MEF_{50,25,15}$ (all about −5%)[6] (0%), and FEF_{75-85} (+5%); n = 198 (132 ETS exposed) F and 393 (251 ETS exposed) M
Brunekreef et al. 1985 [15]	NC (−1 to −7%)	NC (0 to −3%)	NR	decr. PEF (−10 to −16%), MEF_{75} (−9 to 15%); n = 57 (27 ETS exposed)
Hosein and Corey 1986 [16]	NC (+1%)	NR	NR	NC MEF_{25} (−2%), MEF_{75} (−2%); n = 95 (59 ETS exposed)
Svendsen et al. 1987 [17]	decr. (−3%)	NR	NR	decr. in FEV_1 (−5%) for subjects with spouses smoking 1–19 cigarettes/day; −1% for ≥ 20 cigarettes/day; not significant for trend; n = 676 (162 ETS exposed)
Kauffmann et al. 1989 [18]	NC (< −1%)[3]	NC (< −1%)	NR	NC for FEV_1/FVC; NS (< −1%)[3] for FEV_1, FVC, FEV_1/FVC for F over 40 y; n = 726 (451 ETS exposed)

eter examined was FEV_1 which was measured in 17 of the 18 studies listed. Of these 5 show a statistically significant decrement associated with ETS exposure [17, 19, 21, 22, 24] while 12 do not [8–12, 14–16, 18, 20, 23, 25]. Table 1 shows that of the 11 studies that measured FVC 2 report a statistically significant decrement [21, 24] and 9 do not [8–11, 14, 15, 18, 20, 25]. FEF_{25-75} was determined in 5 studies where 3 show a statistically significant decrement [9, 20, 21] and 2 do not [11, 14a, b]. As indicated in the column designated 'other observations' of table 1, PEF was examined in 6 studies [8, 12–15, 21] with statistically significant decrements reported in 3 of these [15, 21]. Also noted in 'other observations' are isolated observations with apparently no consistent pattern, such as decrements of a parameter in a sub-population of a cohort [11, 23]; evidence of gender effects, but not necessarily in the same gender [11, 20, 21]; decrements or no significant change in a variety of other measures (e.g., FEF_{75-85}, $FEV_{1\%}$, MEF_{25}, MEF_{50}, MEF_{75}, air velocity index, or total expiratory time); an anomalous dose-response relationship where the intermediate dose produced a more pronounced effect than the high dose [17]; and associations with ETS at home and not at work and vice versa [20, 21].

Respiratory Symptoms and Disease

Our initial reviews [6, 7] of the epidemiology studies dealing with chronic ETS exposure and respiratory symptoms and disease in adults involved the first 8 studies listed in table 2 [8, 10, 13, 18, 19, 26–28]. Since those reports have appeared we uncovered one additional early report published in 1979 [29] and 15 reports published

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Table 1 (continued)

Study [ref.]	FEV_1	FVC	FEF_{25-75}	Other observations and number of subjects
Hole et al. 1989 [19]	decr. (−3%)	NR	NR	n = 2,455 (1,535 ETS exposed)
Mast et al. 1988 [20]	NC	NC	decr. (−15%)[4]	FEF_{25-75} decr. significant in M only at home, not work; no significant relationship between ETS and flow-volume endpoints in F; n = 133 F and 160 M
Masjedi et al. 1990 [21]	decr. (−7% M) (+1% F)	decr. (−5% M) (< +1% F)	decr. (−15% M) (−9% F)	decr. PEF (−3%) M, NC F (−1% to −5%); significant differences observed for men only[5]; attributed to ETS exposure at work, no significant effects of home exposure; n = 167 (78 ETS exposed) M and 108 (54 ETS exposed) F
Ng et al. 1993 [22]	decr. (−3% to −7%)	NR	NR	n = 1,008 (523 ETS exposed) F, 394 (196 ETS exposed) M
Jaakkola et al. 1995 [23]	NC (< −1%)[6]	NR	NC (−3%)[6]	In sub-population of subjects 25 years or under significant association between cumulative ETS exposure at home and δFEV_1 (−1%)[10] judged to be physiologically unimportant; n = 117 (102 ETS exposed)
Xu and Li 1995 [24]	decr. (−6%)[3]	decr. (−7%)[3]	NR	Several associations between ETS and FEV_1 and FVC failed to achieve statistical significance; n = 502 (382 ETS exposed)
Jedrychowski et al. 1995 [25]	NC	NC	NR	n = 859

NC = No significant change; NR = not reported; F = female; M = male; decr. refers to a statistically significant decrease, incr. refers to statistically significant increase

1 Number in parentheses indicates magnitude of change (in %) when available.
2 Magnitudes estimated from graphs.
3 Magnitudes estimated from residuals.
4 Data available for men only.
5 Some statistical discrepancies (i.e., significance only in selected subgroups).
6 Longitudinal study, decrement in function estimated from maximal effect/year/pack of cigarettes/day exposure over period of 8 years.

since 1990 [22, 25, 30–42], accounting for the total of 24 studies appearing in table 2.

As shown in table 2, 15 of 24 studies report some statistical association between chronic ETS exposure and a clinical symptom or disease [18, 22, 25, 26–32, 34, 36–38, 42]. However, as exemplified below there is little consistency from one report to the next with regard to the specific endpoint involved. Cough appears as an endpoint in 9 studies. Of these 2 report a statistically significant association [22, 31] and 7 do not [8, 10, 13, 18, 30, 33, 40]. Of the 9 studies reporting on phlegm or expectoration, 3 indicate a statistically significant association [27, 30, 31] while 6 do not [8, 10, 18, 19, 22, 33]. Of the 10 studies reporting on dyspnea or shortness of breath as an endpoint, 6 report an association [18, 22, 25, 27, 31, 38] and 4 do not [13, 19, 33, 40]. Three [26, 37, 38] of the 6 studies [22, 26, 35, 37, 38, 42] in which bronchitis is the endpoi are statistically associated with ETS exposure. Eviden of asthma incidence, exacerbation or symptoms (e.; wheeze) are dealt with in 18 papers (marked by asterisl Of these 8 indicate a statistically significant associati [18, 22, 29, 32, 34, 36–38] and 10 do not [8, 10, 13, 25, 3 35, 39–42].

Factors Affecting the Outcome of Epidemiological Studies

As shown in tables 1 and 2, respectively, there is consistent epidemiology evidence that chronic ETS ex sure impairs pulmonary function or increases the pre lence of respiratory symptoms and diseases in adults. T is in agreement with our earlier conclusion based u fewer studies [7, 8]. No consistent association from

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Table 2. Epidemiologic studies of ETS exposure and respiratory symptoms and disease in adults

Study [ref.]	Findings and number of subjects
Schilling et al. 1977 [8][1]	No association with cough, phlegm, wheeze[2]; n = 252 (114 ETS exposed)
Simecek 1980 [26]	Increased symptoms of bronchitis by 10–20%[3]; n = 57,217 F, 23,473 M
Comstock et al. 1981 [10][1]	No association with chronic cough (RR = 1.0 M, 0.2 F), chronic phlegm (0.9 M, 0.7 F), chronic cough + phlegm (1.3 M, 0.3 F), wheeze (1.0 M, 1.5 F), breathlessness (1.1 M, 1.8 F), chest illness (0.9 M, 1.0 F); n = 426 (95 ETS exposed) M and 113 (36 ETS exposed) F
Lebowitz 1984 [13][1]	No association with cough, rhinitis, wheeze, shortness of breath[2]; n = 229
Gillis et al. 1984 [27]	Significant association (RR) with persistent spit (1.4), dyspnoea (1.6), hypersecretion (1.7) in M and dyspnoea (1.5) in F; no association with infected spit (1.3) in M, persistent spit (1.1), and hypersecretion (1.2) in F[4]; n = 827 (310 ETS exposed) M, 1,917 (1,704 ETS exposed) F
Kalandidi et al. 1987 [28]	Increased risk (RR, 90% CI) of COPD (2.5, 1.3–5.0 for ≤1 pk/day; 1.5, 0.8–2.7 for >1 pk/day); n = 282 (166 ETS exposed)
Kauffmann et al. 1989 [18][1]	No association (OR, 95% CI) with chronic cough (1.1, 0.6–2.1 US; 1.3, 0.8–2.4 France), chronic phlegm (1.7, 0.7–3.8 US, 0.8, 0.3–2.0 France), dyspnoea (1.3, 0.7–2.6 US, 1.2, 0.9–1.6 France), and wheeze (1.0, 0.7–1.4 France); in US population, borderline significant association for wheeze (1.3, 0.97–1.9). In French population, 'increased' prevalence of dyspnoea in women ≥40 y (1.45, p = 0.1); n = 726 (451 ETS exposed) US, n = 2,298 (1,470 ETS exposed) France
Hole et al. 1989 [19]	No significant increased risk (RR, 95% CI) of infected sputum (1.3, 0.8–2.4), persistent sputum (1.2, 0.9–1.7) dyspnoea (1.1, 0.8–1.5) or hypersecretion (1.2, 0.8–1.8); n = 2,555 (1,538 ETS exposed)
Shephard et al. 1979 [29][1]	Report of wheezing (11%) and rhinorrhoea (19.3%) when exposed to ETS; n = 182 (all exposed to ETS)
Schwartz and Zeger 1990 [30]	Associated with increased risk (RR, 95% CI) of an episode of phlegm (1.4, 1.1–1.9) but not cough[2]; n = 100 (approximate)
White et al. 1990 [31]	Increased risk (RR)[4] of cough (2.8), phlegm (3.2), shortness of breath (4.5), eye irritation (2.8), chest colds (4.3), and lost workdays due to chest colds (2.6); n = 80 (40 ETS exposed)
Cummings et al. 1991 [32][1]	Majority of subjects (74–82%) with a medical history of atopy, asthma, or other upper and lower respiratory disease reported being 'bothered by smoke'; n = 376 (all exposed to ETS)
Ng et al. 1993 [22][1]	Increased risk (RR, 95% CI) of cough (3.8, 1.8–8.1), wheeze (2.7, 1.2–5.9), and breathlessness on exertion (1.8, 1.3–2.6); no significant association for phlegm (2.3, 0.9–5.6), chronic bronchitis (2.3, 0.96–5.3), and physician diagnosed asthma (1.6, 0.7–3.7)[7]; n = 1,282 (663 ETS exposed)
Pope and Xu 1993 [33][1]	No significant association (OR, 95% CI) with chest illness (1.0, 0.5–1.9), cough (1.9, 0.7–4.9), phlegm (2.1, 0.9–5.0), shortness of breath (1.5, 0.4–5.5), or wheeze (1.0, 0.3–3.7)[5]; n = 633 (451 ETS exposed)

study to the next is evident between such exposure and a specific spirometric measure or respiratory symptom and disease. The inconsistency of data may reflect absence of such associations or methodology problems inherent in pulmonary function measurement (for studies dealing specifically with spirometry) or the epidemiology method used (for studies of pulmonary function and prevalence of respiratory illness and disease).

As previously discussed, certain considerations apply for epidemiology studies dealing with pulmonary function [7, 8]. Although somewhat insensitive, FEV_1 is regarded as a reasonably reproducible measurement of expiratory airflow in which abnormal measures of this parameter are predictive of certain types of pulmonary dysfunction and disease [43]. On the other hand, the suggestion that abnormalities in FEF_{25-75} are indicative of disease and dysfunction of small bronchioles (under 2-

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Table 2 (continued)

Study [ref.]	Findings and number of subjects
Greer et al. 1993 [34][1]	Increased risk (RR, 95% CI) of asthma (1.5, 1.2–1.8) associated with workplace ETS exposure over a 10-year period (longitudinal study); n = 3,914 (1,647 ETS exposed)
Robbins et al. 1993 [35][1]	No significant association (RR, 95% CI) between ETS exposure during adulthood (1.3, 0.9–1.8) or childhood (1.1, 0.7–1.8) and airway obstructive disease (asthma, chronic bronchitis, and emphysema); significant association (1.7, 1.3–2.2) with ETS exposure during adulthood + childhood [same cohort as Greer et al., 1993]; n = 3,914 (1,856 ETS exposed)
Bottai et al. 1994 [36][1]	Associated with increased risk (RR) of skin test sensitivity (1.33) and subjective respiratory symptoms[2] but not pulmonary function[2] or bronchial reactivity to methacholine[2]; n = 305 (133 ETS exposed)
Dayal et al. 1994 [37][1]	Increased risk (OR, 95% CI) of obstructive respiratory disease (asthma, chronic bronchitis, or emphysema) (1.9, 1.2–2.9); n = 876
Leuenberger et al. 1994 [38][1]	Increased incidence (OR, 95% CI) of wheezing apart from colds (1.9, 1.4–2.7), bronchitis symptoms (1.6, 1.2–2.1), chronic bronchitis (1.7, 1.3–2.2), dyspnoea on exertion (1.5, 1.2–1.8), physician diagnosed asthma (1.4, 1.0–1.9); no significant association for allergic rhinitis including hayfever and atopy (1.0, 0.8–1.3); n = 3,494 (1,047 approximate)
Hong et al. 1994 [39][1]	No significant association (OR, 95% CI) with asthma morbidity (1.2, 0.7–1.9); n = 787 (384 ETS exposed)
Ostro et al. 1994 [40][1]	No significant association (OR, 95% CI) with cough (1.3, 0.8–2.1), shortness of breath (1.2, 0.97–1.4), or nocturnal asthma (1.1, 0.7–1.6); significant association with restricted activity (1.6, 1.1–2.5); n = 164 (15 ETS exposed[6])
Flodin et al. 1995 [41][1]	No significant association (OR, 95%) with incidence of asthma (1.5, 0.8–2.5); n = 383 (uncertain if all were non-smokers)
Jedrychowski et al. 1995 [25][1]	In elderly women ETS exposure associated (OR, 95% CI) with dyspnoea on exertion (2.2, 1.5–3.4) but not asthma (0.5, 0.2–1.1); n = 1,255 (129 ETS exposed)
Leuenberger et al. 1995 [42][1]	In subjects reporting respiratory symptoms, no significant negative association (RR) between ETS exposure at work and length of intervals without asthma symptoms (wheeze, dyspnoea, or chest tightness apart from cold) (1.1); significant negative association between ETS exposure at work and intervals without bronchitis symptoms (cough, phlegm apart from colds) (1.31); n = 1,492

RR = Relative risk; OR = odds ratio; CI = confidence intervals.

[1] Those studies dealing with asthma symptoms, incidence or exacerbation.

[2] Magnitude of risk not reported.

[3] Estimated from graph.

[4] RR or OR calculated from data presented in paper (e.g., prevalence rates).

[5] More than one value presented for each endpoint on the basis of intensity of ETS exposure. Highest RR or OR usually presented.

[6] Number of subjects ETS is an average based upon the proportion exposed each day.

3 mm in diameter) is controversial [44, 45]. Furthermore, FEF_{25-75} and related parameters are reported to have considerably more variability than FEV_1 from test to test in the same subject [43]. Thus the clinical significance of statistically significant differences in the latter parameter may be suspect. Furthermore, determination of normal and abnormal levels of pulmonary function in a particular subject requires comparisons between observed and predicted values which have been adjusted for age, height, and gender of the subject by a derived formula, since these variables strongly influence lung function [43, 45]. Other important considerations in spirometric testing are the expertise of the individual administering the test, the type of equipment employed, and the attitude of the subject undergoing evaluation [43].

A lack of consistency in the relationship between ETS exposure and pulmonary function in adults is also evident in the five studies in which FEV_1 and FEF_{25-75} are mea

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sured simultaneously (table 1). Of these, only one indicates a decrement in both measures [21], 2 report a decrement in FEF_{25-75} without one in FEV_1 [9, 20], and 2 report no change in either measure [11, 14]. When a decrement in a particular measure is observed, it is of small magnitude, generally ranging from 3 to 15%. Even then the individual spirometric values for exposed groups are within the normal range for pulmonary function (i.e., relative to the normal predicted value). Thus, it is questionable whether the statistically significant decrements in pulmonary function associated with ETS exposure that appear in these isolated studies are meaningful in terms of clinically significant effects on pulmonary function.

The fundamental instrument of the epidemiology process is the questionnaire. This provides data concerning smoking status, ETS exposure status, respiratory symptoms and/or diseases and potential confounding variables which are also a source of variation in these studies. The questionnaires varied from study to study in their standardisation, level of validation and the ways in which they were administered. In contrast to the objective endpoints used in the studies of table 1, in those of the epidemiology studies listed in table 2, respiratory symptoms and/or diseases, were provided by the subjects and lacked objective verification of the subjects symptoms (e.g., medical records, etc.). In addition to the subjective component, information on these endpoints was provided by individuals lacking medical expertise which could also provide an element of inaccuracy in this information. Other flaws in the collection of clinical endpoint data were the lack of consistency in adhering to diagnostic definitions of a specific disease such as asthma, as well as the failure in many cases to differentiate one specific disease from another (e.g., asthma from COPD and other respiratory diseases).

In all of the studies in question, classification of ETS exposure status lacked verification with a bio-marker, such as body fluid concentration of the nicotine metabolite, cotinine. The surrogate most commonly used for ETS exposure, spousal smoking status, represents a major source of misclassification of exposure. In this situation non-smoking individuals married to smokers may actually receive little or no ETS exposure if their spouses avoid smoking in the subject's presence, while a non-smoker married to a non-smoker (usually classified as unexposed) could receive exposure through other sources (e.g. work, social activities) [46]. Such error, designated as non-differential, tends to underestimate the impact of an effect of ETS [47].

On the other hand, spousal smoking as a surrogate for ETS exposure can be a source of differential bias which can lead to overestimation of the effects of ETS. When smokers or former smokers in the study population are misclassified as non-smokers, they bring to a population the increased risk of pulmonary dysfunction or respiratory illness and disease associated with their active smoking. Marital concordance, or the tendency of smokers to marry smokers and non-smokers to marry non-smokers coupled with misclassification of smokers as non-smokers is a well recognised source of differential bias in the case of spousal smoking and lung cancer [5, 47] and may produce a similar effect in epidemiology studies of non-cancerous effects on the respiratory system. As discussed previously, spousal smoking and related surrogates of ETS exposure (e.g., household smokers) may also be associated with confounding variables that affect the outcome of an epidemiology study. There is indication of this in the reports of positive associations between the extent of ETS exposure and occupational hazards, marijuana use and alcohol consumption. Also, non-smoking women married to non-smokers tend to have better lifestyle health habits than those married to smokers [46, 48].

As discussed previously, confounding variables which may exaggerate or attenuate an apparent association between ETS and a particular endpoint can affect the outcome of an epidemiology study and serve as a possible source of inconsistency in epidemiology studies of respiratory effects of chronic ETS in adults [7, 8]. In general, the more recent studies of pulmonary function and clinical endpoints have done little to improve the situation with their treatment of confounding variables. There is inconsistency from study to study with regard to the treatment of confounding variables and many of the studies fail to consider potentially important factors. In the case of exacerbation of asthma, for example, numerous confounding variables have been recognised such as gastro-oesophageal reflux, hormone (especially oestrogen) therapy, other occupational exposures, psychological and emotional factors, exposure to infectious agents, exposure to environmental allergens, exposure to other environmental irritants, use of various prescription and over-the-counter drugs, food additives, changes in weather, exposure to cold air, exercise, pregnancy, other endocrine factors, age, gender, environmental changes, relative humidity, socio-economic factors, ethnicity and normal diurnal fluctuations, among others [49–52]. In the studies in table 2 pertaining to asthma incidence, exacerbation or symptoms, where only 8 of 18 report a statistically significant association, relatively few of these confounding variables are addressed.

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Experimental Studies of Acute Effects of ETS Exposure

The effects of acute ETS exposure have involved spirometric measures prior to, during, and after exposure of both normal and asthmatic subjects to machine generated tobacco smoke in an exposure chamber. Unlike most of the chronic epidemiology studies, the levels of acute ETS exposure in these experimental studies have usually been quantitated by such environmental markers as carbon monoxide and respirable suspended particles. The levels attained in these acute exposure studies are usually equivalent to or exceed those found in real-life, smoke-polluted environments, such as bars [4, 5]. In some of the studies, broncho-provocation or bronchial challenge was performed in which the subjects inhaled graded doses of substances known to produce bronchoconstriction (e.g., methacholine, histamine, cold air) to determine the threshold dose required to produce bronchoconstriction. Such a dose is usually a reflection of genetic effects, environmental agents (e.g., irritants, allergens), or predisposition to asthma [43].

Normal Adults

As previously discussed, 5 of 6 studies reported that exposure of normal subjects to machine generated smoke (up to levels of 40–50 ppm CO) for up to 2 h, and in 1 case, including exercise during exposure, failed to produce statistically significant effects on spirometric parameters in normal subjects, although there were some complaints of eye irritation, nasal discharge and/or stuffiness and cough, but not sore throat, shortness of breath, chest tightness, wheezing, dizziness or headache [53–57]. The sixth study reported that a 30-min exposure to machine-generated tobacco smoke significantly decreased PEFR accompanied by frequent complaints of eye irritation, tearing, dizziness, headaches and chest tightness. This study lacked data on environmental markers of exposure, other than room size and mention of the fact that smoke was produced from 8 cigarettes [12]. Thus, the significance of this isolated report relative to the other negative observations cannot be determined. One additional study, published since our last review, failed to show an effect on pulmonary function of non-asthmatic individuals after 4 h of smoke exposure at levels of ETS up to 13.3 ppm CO [58]. Thus, most of the studies suggest that acute ETS exposure, while serving as an irritant to the upper respiratory tract, failed to adversely affect pulmonary function in non-asthmatic individuals.

Bascom et al. [59] studied responses of the upper respiratory tract of 29 healthy adults to varying concentrations (0, 1, 5 and 15 ppm CO) of side stream smoke for 2 h. On the basis of a reported history of ETS-induced rhinitis, subjects were classified either as ETS-sensitive (ETS-S) (n = 13) or ETS-non-sensitive (ETS-NS) (n = 16). A questionnaire was used by the subjects to rate their perceptions of odour and various symptoms (eye irritation, nose irritation, nasal congestion, runny nose, chest tightness, cough, headache and number of sneezes), as well as heart palpitation as a sham symptom. Nasal responses were objectively measured by acoustic rhinometry (nasal dimensions) and posterior rhinomanometry (nasal resistance). Both groups showed statistically significant exposure responses for eye irritation and odour. Nasal congestion, rhinorrhoea and cough in both groups required side stream smoke exposures of 15 ppm CO. A significant increase in nasal resistance was observed in both groups after 2 h of side stream smoke at 15 ppm CO. Some differences were observed between ETS-S and ETS-NS subjects, however. Significant responses were reported for headache in ETS-S subjects and for nose irritation for ETS-NS subjects. ETS-S subjects reported significantly greater headache, eye irritation, odour, and runny nose than ETS-NS at the 1 ppm CO level but not at higher levels of side stream smoke. On the other hand, differences were observed between the two groups which make little sense. For example, chest tightness was evident at 15 ppm CO, only in ETS-NS subjects and not reported in ETS-S subjects. Decreased nasal volume occurred at 1 ppm CO in ETS-NS subjects but not ETS-S subjects. Although heart palpitation was not evident in either group at any level of exposure, it is difficult to discern from this study which of the responses (subjective or objective) represented physiological or psychological reactions to tobacco smoke exposure. Thus, the significance of this study is in question.

Asthmatic Adults: Acute Exposure

The first 5 papers listed in table 3 [55–57, 60, 61] were discussed in our previous reviews [7, 8]. Two reports indicate a decline of baseline pulmonary function [55, 61] and 2 show no such decline [56, 60]. In the fifth report, 7 subjects showed a response to ETS while 14 did not [57]. Variability was also indicated in 2 of the initial studies in which broncho-provocation was tested. One study indicated that ETS exposure increased broncho-reactivity [61] while the other indicated a decrease in broncho-reactivity [56].

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As discussed previously [7, 8], variation in the results among the initial 5 studies could have several explanations. One such explanation could be different levels of severity of underlying asthma from one study to the next. The differences in broncho-reactivity in 2 could reflect the use of broncho-provocation agents, methacholine and histamine (table 3), that have different mechanisms of action. It is known that asthmatic episodes can evoke psychological and emotional stimuli [62–65], even in response to odours [66]. Therefore, flaws in the protocol of some of the foregoing studies could have evoked such non-specific asthmatic responses. Among these study flaws are the lack of a control exposure in the study of Dahms et al. [55] and the non-random design in the study of Knight and Breslin [61]. On the other hand, the possibility of non-specific asthmatic responses may have been minimised by the random exposure protocol of Shephard et al. [60] and use of goggles (to prevent eye irritation) in the study of Wiedemann et al. [56]. It is unlikely that the intensity of ETS exposure in the initial 5 studies accounted for the variability, since the 2 negative studies of this series had either the longest duration [60] or highest level of ETS [56] (table 3).

In the fifth study of the initial set of reports, all 21 subjects claimed to be sensitive to ETS (i.e., they believed that ETS exposure would cause exacerbation of their asthma) and 19 were documented to be atopic (i.e., common, IgE immunoglobulin-mediated allergy) [57]. Five of the 7 responsive subjects developed a significant (defined as greater than 20%) decline in FEV_1 after exposure only at the higher level of ETS exposure (13.3 ppm CO) to evoke a response. Furthermore, in all subjects the decrease in FEV_1 occurred only during the 2nd h of the 2-hour exposure while no change was observed during the 1st h of exposure. In all cases, the airflow obstruction was readily reversed with the administration of an inhaled bronchodilator. The authors suggested that a subset of asthmatics were intolerant to ETS. However, the mechanism for this intolerance was apparently not allergic, since no correlation was observed in these subjects between skin or serologic reactivity to tobacco leaf antigen and the occurrence of airflow obstruction with exposure to tobacco smoke.

Since our previous review, 10 additional studies have examined acute ETS exposure and pulmonary function in adult asthmatics, as listed in table 3. The next 3 studies on the list [58, 67, 68] were published by the same group as that of Stankus et al. [57]. The levels of ETS exposure were the same as that of the original study of this series, whereas the duration of exposure was extended from 2 to 4 h. Consistent with the original report, these subsequent studies all show that only a subset of the general population appear to be intolerant to smoke exposure, ranging in proportion from 33% (i.e., 5 of 15 subjects) to 12% (7 of 58 subjects). In fact, it appeared that in these subsequent studies the ETS-responsive subjects were for the most part the same individuals that appeared in the original study.

In one study of Menon et al. [58] the FEV_1 decrease occurred after 1–2 h of ETS exposure. There were no 'late' reactions noted. The authors pointed out that this absence of late reactions differs from the IgE-mediated reactions seen with classic allergen challenge. They also reported that, in those subjects who reacted to tobacco smoke exposure with airflow obstruction, such a reaction could be prevented by pre-treatment with inhaled albuterol (a bronchodilator) and/or inhaled cromolyn (an anti-inflammatory agent). No correlation was found between bronchial reactivity to tobacco smoke and bronchial reactivity to methacholine. While 5 of 31 subjects exhibit a >20% decrease in FEV_1, 10 of 31 subjects exhibit an increase in bronchial reactivity to methacholine at 6 h [67]. This group was unable to demonstrate any correlation between immunologic (skin and serologic immunologic tests with tobacco leaf extract and tobacco smoke extract) and pulmonary reactions in these subjects, inconsistent with what would be expected in an allergen reaction [68]. Thus, their observations did not support tobacco smoke allergy as a mechanism of the reaction, consistent with their original conclusion [57].

The next 4 studies listed in table 3 [69–71, 73] represent a series of studies from another group which for the most part suggest that asthmatics exhibit little or no response to acute ETS exposure. Magnussen et al. [69] reported no significant differences in lung function or airway responsiveness to methacholine challenge between exposure to ambient air or ETS, even though smoke exposure was associated with eye and nasopharyngeal irritation. In a subsequent report, Jorres and Magnussen [70] essentially confirmed their previous findings. In the third study, subjects were characterized as having 'mild' asthma and medication was withheld for at least 8 h before the tests. Exposure was from 7 to 10 p.m., and spirometry was performed prior to, at half-hour intervals during exposure and at several times following exposure until 7 a.m. Methacholine was also administered prior to and after exposure. A fall in FEV_1 was observed after both ETS (10.9%) and sham exposures (6.5%). A small increase in bronchial reactivity to methacholine after both sham and ETS exposure was also observed, with a slightly greater degree of reactivity after ETS than after sham exposure [71]. Spontaneous nocturnal and early morning decreases

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Table 3. ETS and asthma in adults: human exposure studies

Study [ref.]	Number of subjects	Exposure level CO ppm	Duration, h	Results
Shephard et al. 1979 [60]	14	24	2	NSC FEV_1 (+1%), V_{max25} (+25%) and V_{max50} (0%)
Dahms et al. 1981 [55]	10	15–20	1	21% decr. mean FEV_1
Knight and Breslin 1985 [61]	6	20–25	1	3/6 9–27% decr. FEV_1; 6/6 incr. histamine BR
Wiedemann et al. 1986 [56]	9	40–50	1	NSC FEV_1 (<–1%), V_{max50} (–1%); 8/9 decr. methacholine BR
Stankus et al. 1988 [57]	21	8.7 13.3	2 2	2/21 >20% decr. FEV_1; 7/21 >20% decr. FEV_1
Menon et al. 1991 [58]	15	13.3	4	5/15 >20% decr. FEV after 1–2 h; protected by albuterol or cromolyn
Menon et al. 1992 [67]	31	13.3	4	5/31 >20% decr. FEV; 10/31 incr. methacholine BR
Musmand et al. 1993 [68]	58	13.3	4	7/58 >20% decr. FEV_1; mean onset 1.8 h
Magnussen et al. 1992 [69]	18	20	1	NSC FEV_1 (–3%) and airway resistance (–5%) or BR to methacholine
Jorres and Magnussen 1992 [70]	24	20	1	NSC FEV_1 (–4%) and airway resistance (–6%) or BR to methacholine
Nowak et al. 1993 [71]	17	20	3	10.9% decr. in nocturnal FEV_1 (6.5% with sham exposure); small incr. methacholine BR
Nowak et al. 1995 [73]	10	22	3	NSC respiratory flow rates, visual bronchoscopy; BAL/NAL
Gurk et al. 1991 [74]	20	35–40	1	4% decr. mean FEV_1; 13% incr. airway resistance; NSC histamine BR overall
Danuser et al. 1993 [75]	10	0–32	2 min	direct delivery to mouthpiece; multiple exposures; 9/10 decr. FEV_1 (5/10 >10%, 1/10 >20%); no dose-response
Bascom et al. 1991 [77]	10	45	0.25	<7% decr. PFT parameters

NSC = No significant change; BR = bronchial reactivity; PFT = pulmonary function test.

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in respiratory flow rates and increases in bronchial reactivity are common phenomena in asthmatics [43, 49, 72] and the spirometric measures and bronchial reactivity observed in this study were within the range of spontaneous variation for asthmatics at night and in the early morning [43]. Thus, these changes were probably neither physiologically significant nor clinically relevant. The final paper of this series reported no significant changes in spirometry during or after ETS exposure, as well as no significant effects of ETS exposure on visual bronchoscopic scoring, bronchial lavage (BAL) cells or mediators, or nasal lavage (NAL) mediators [73]. The authors concluded that there was no evidence of an inflammatory effect from acute ETS exposure.

Gurk et al. [74], who exposed subjects to levels of ETS usually higher than most of the preceding studies (CO level of 35–40 ppm) reported a 4% decrease in mean FEV_1 and a 13% increase in specific airway resistance post-exposure compared to pre-exposure (table 3). Since these statistically significant differences were within the range of reported individual variability of these parameters [43], they are probably neither physiologically significant nor clinically relevant. Furthermore, no change in histamine bronchial reactivity as a result of ETS exposure could be detected in the group as a whole. The authors state, however, that in a sub-group of 10 subjects who had a greater than 5% decrease in FEV_1 there was a small increase in bronchial reactivity, which they indicate was statistically significant. No correlation was found between pre-exposure bronchial reactivity to histamine and bronchial reaction to tobacco smoke exposure.

Danuser et al. [75] used a somewhat different method of tobacco smoke challenge than other investigators. Subjects with previously documented hyperreactive airways were challenged with machine-generated sidestream smoke delivered directly to an inhalation tube at varying concentrations (0, 2, 4, 8, 16 and 32 ppm CO) for 2 min per dose. A dose-related increase in subjective symptoms of cough/dry throat, chest tightness and dyspnea was reported. Although a decrement in FEV_1 with smoke exposure occurred in 9 of 10 subjects, it exceeded 20% in only 1 of the 10. Changes in FEV_1 of less than 20% are of doubtful physiological significance or clinical relevance and are within the range of expected intra-individual variation for this spirometric parameter [43]. Furthermore, the decrement was most marked at a CO concentration of 2 ppm and the FEV_1 remained at a plateau at higher smoke levels. An editorial that accompanied this paper indicated that the authors did not completely answer the question of the relative contributions of physical and psychological responses. The subjective symptoms exhibited a dose-response relationship, whereas the objective physiological reactions did not (table 3) [76].

Bascom et al. [77] exposed historically ETS-S subjects to sidestream smoke at a CO concentration of 45 ppm for 15 min. The ETS-S subjects reported significant upper and lower respiratory symptoms compared to controls and a significant increase in nasal airflow resistance. Decrements (less than 7%) in pulmonary function parameters were noted. Changes of this magnitude are not likely to be physiologically significant or clinically relevant [43]. There were no significant differences in concentrations of inflammatory mediators in nasal lavage fluid in ETS-S subjects compared to controls. These results were interpreted by the authors to indicate that there is an increased responsiveness to ETS in historically smoke-sensitive subjects but that an allergic, IgE-mediated mechanism is unlikely (table 3).

In summary, the experimental studies suggest that acute exposure to high levels of machine-generated ETS does not consistently evoke adverse physiological changes in the pulmonary system of most asthmatics. The observations of Stankus et al. [57, see also 58, 67, 68] suggest that a small sub-set of asthmatics may respond to acute exposure with a decrement in respiratory flow rate of 20% or greater as well as increased responsiveness to bronchoconstrictors. The mechanism for this responsiveness is subject to speculation. As noted in the studies listed in table 3, the observations of Bascom et al. [77] and a series of studies by Stankus and associates [57, 58, 67, 68] essentially rule out the involvement of an IgE-mediated allergic mechanism. Similar results have also been reported by Gleich and Welsh [78] and McDougall and Gleich [79].

In view of the lack of evidence of an allergic mechanism responsible for the acute response of selected asthmatics to ETS exposure, other possibilities are suggested in the literature. The observations of Urch et al. [80] suggested that a pulmonary response to ETS also correlated with indices of suggestibility. In a subsequent report [81], this group analysed relationships between various exposure indices, subjective symptoms and the subjects' perceived severity of exposure. They noted that factors that appeared to significantly influence a subject's perception of exposure included the characteristics of cigarette smoke, eye irritation, previous ETS exposure and the individual's threshold of response. That emotional and psychological factors can trigger increases in airflow obstruction and clinical exacerbation in asthmatics is well documented, as noted previously in this review [63, 64, 82–85]. Recent work suggests that anxiety disorders and

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probably other psychological problems are more common in asthmatic patients than in the population at large and that the disorder of asthma may, in and of itself, predispose patients toward the development of anxiety disorders [86, 87]. In virtually all of the challenge studies involving tobacco smoke exposure in asthmatics, it has been difficult, if not impossible, to control for confounding by psychogenic influences brought into play by the distinctive odour of tobacco smoke and the individual's expectations [76].

Similarly, Moschandreas and Relwani [88] found that visual contact with a tobacco smoke source affected the perception of a variety of odour parameters, including changing the nature of the perception toward unpleasant and increasing the number of subjects who perceived a tobacco odour. In addition, Thompson et al. [89] reported that perception of and being bothered by tobacco smoke in the workplace was affected by smoking policy, smoking status, age, gender, living with a smoker and occupation. In addition to their relevance to the issue of psychogenic factors and exacerbation of asthma in experimental challenge studies, these results may also be important relative to the issue of confounding variables affecting the results of epidemiological studies discussed in table 2.

Summary and Conclusion

Epidemiology studies of chronic ETS exposure and pulmonary dysfunction and the incidence of respiratory symptoms and diseases in adults fail to demonstrate consistent associations. This inconsistency could either reflect absence of such an association or problems of methodology. Among the possible methodology problems are reliability of spirometric measurement, lack of verification of clinical endpoints, errors in classification of subjects as to smoking and ETS exposure status and inappropriate control of potential confounding variables. Experimental studies of the effects of acute ETS exposure suggest that ETS does not consistently evoke adverse pulmonary effects in normal subjects and the majority of asthmatics. A sub-set of asthmatics may exist that respond to ETS exposure with a decrement in FEV_1 and increased responsiveness to bronchoconstrictors. The mechanism of this responsiveness does not appear to be allergic in nature and is subject to speculation.

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